

Case Report

Aspergillus Pseudomembranous Tracheobronchitis Complicating Treatment of COPD Exacerbations

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ABSTRACT

Aspergillus pseudomembranous tracheobronchitis is an uncommon form of invasive aspergillosis that affects immuno-compromised hosts. We describe the clinical and radiological features of this form of invasive

aspergillosis occurring in two patients with severe COPD as a complication of treatment with corticosteroids and broad spectrum antibiotics.

KEY WORDS: aspergillosis, COPD, tracheobronchitis

INTRODUCTION

Aspergillus pseudomembranous tracheobronchitis is a form of invasive pulmonary aspergillosis that is limited to the tracheobronchial tree. Aspergillus hyphae invade the airways and form plugs that can lead to airway obstruction. It occurs most commonly in neutropenic patients receiving chemotherapy but has also been described following organ transplantation, viral infections (particularly influenza), diabetes mellitus, renal and hepatic failure and in patients with acquired immunodeficiency syndrome. In addition to these underlying diseases, a history of treatment with corticosteroids and antibiotics is common. Patients usually present with dyspnea, cough and wheezing. They occasionally expectorate mucus plugs or tracheobronchial casts. The diagnosis is confirmed by demonstrating fungal invasion of the airways. The condition is associated with a high mortality rate despite treatment. There are three previous case reports of aspergillus tracheobronchitis occurring in patients with COPD. We report two further cases, describe their clinical and radiological features and speculate on the role of corticosteroid therapy, broad spectrum antibiotics and possibly antecedent viral respiratory tract infection in the occurrence of this rare, but frequently lethal, complication of COPD exacerbations.

Case 1

A 67-year-old female cigarette smoker with known COPD presented to hospital in the fall of 1998 with increasing shortness of breath. A chest

radiograph showed evidence of hyperinflation of the lungs but no infiltrates. She was admitted with a diagnosis of COPD exacerbation and was treated empirically with bronchodilators, systemic corticosteroids and cefuroxime. Erythromycin was added later because of failure to improve. Spirometry showed an FEV1 of 0.65L (31% predicted).

The patient continued to deteriorate. She developed herpes labialis and a painful red eye, subsequently confirmed to be herpes simplex keratitis. She also had oral candidiasis. A follow-up chest radiograph 12 days later showed poorly defined bilateral nodular opacities (Fig. 1). High resolution CT of the chest (Fig. 2) demonstrated extensive bilateral centrilobular nodular and branching linear opacities (tree-in-bud pattern). Also noted were a few randomly distributed nodules measuring 5 to 10 mm in diameter and patchy bilateral ground glass opacities. Bronchial wall thickening was present involving mainly the segmental and subsegmental bronchi of the upper lobes. Bronchoscopy revealed pharyngeal candidiasis and extensive membranous, slightly hemorrhagic exudates throughout the trachea and proximal main-stem bronchi. The membrane was adherent and attempted suction caused slight bleeding. The washings showed the pseudomembrane to contain *Aspergillus* and cultures grew *Aspergillus fumigatus*. Transbronchial and endobronchial biopsies confirmed the presence of inflammatory pseudomembranes within which were fungal elements morphologically



Fig. 1: Chest X-ray of case 1 showing poorly defined bilateral nodular opacities

consistent with *Aspergillus*. The mucosa and submucosa were inflamed and there was squamous metaplasia. Serum immunoglobulin level showed a pattern consistent with acute phase reaction but no evidence of immunoglobulin deficiency. A diagnosis of *Aspergillus* pseudomembranous tracheobronchitis was made. The disease was differentiated from allergic bronchopulmonary aspergillosis (ABPA) by the following: (1) the absence of peripheral eosinophilia, (2) the absence of the appearances of ABPA on endobronchial biopsy (e.g. allergic mucin and eosinophils), (3) the presence of inflammatory pseudomembranes that are not known to occur with ABPA, and (4) the progression of the disease despite high doses of systemic steroids. Amphotericin B was commenced and the patient was transferred to the intensive care unit for increasing shortness of breath and stridor. She improved significantly on Amphotericin B but when switched to oral itraconazole she deteriorated and Amphotericin B was re-started. Two months after admission, she coughed up a large grayish tracheobronchial cast, histology of which revealed organized inflammatory pseudomembranes. The patient improved gradually and was discharged from hospital after a three-month stay. She had received a total dose of 2705 mg of Amphotericin B and was discharged on no antifungal therapy.

One year later the patient was readmitted to hospital with increasing shortness of breath. Sputum cultures grew *Aspergillus*, and a CT chest showed areas of bronchiectasis and new nodular opacities. She was presumed to have reactivation of invasive aspergillosis and was started on treatment

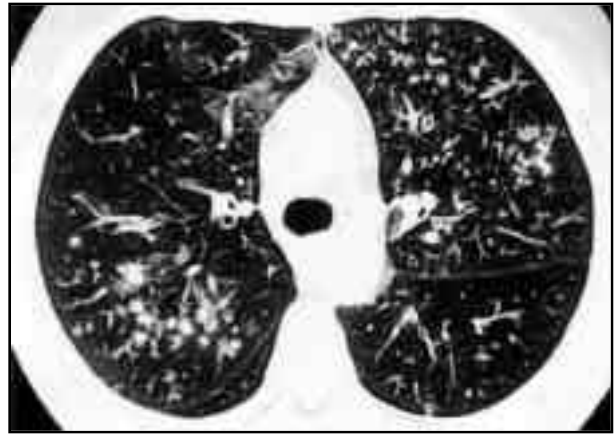


Fig. 2: HRCT of case 1 showing centrilobular nodular opacities (thin arrows) and branching linear opacities (thick arrow) (tree-in-bud pattern)

with itraconazole. Despite treatment she developed worsening respiratory failure and died. Permission for autopsy was declined.

Case 2

A 74-year-old male with COPD presented with shortness of breath and cough. A chest radiograph showed hyperinflation but was otherwise unremarkable. Peripheral white blood cell count was normal. Spirometry revealed an FEV1 of 0.58l (23% predicted). He was admitted to hospital with a diagnosis of COPD exacerbation and was treated with bronchodilators, cefuroxime, erythromycin and systemic corticosteroids. Cefuroxime was later switched to cefotaxime. Despite five days of treatment, the patient's condition progressed to acute respiratory failure necessitating transfer to the intensive care unit and endotracheal intubation. He developed leukocytosis with a neutrophilic predominance. A repeat chest X-ray showed diffuse reticulonodular infiltrates. A high resolution CT chest revealed extensive bilateral centrilobular nodular and branching linear opacities and bronchial wall thickening. Sputum culture was positive for *Aspergillus fumigatus*. On bronchoscopic examination, copious thick white secretions were observed throughout the entire tracheobronchial tree with adherent plaques in the right main-stem bronchus and pseudomembranes more distally in the right lower lobe. Bronchoscopic biopsies showed numerous fungal hyphae (*aspergillus*) within material consistent with pseudomembranes. Bronchial washings grew *Aspergillus fumigatus*. Both the bronchoscopy findings and the CT appearances were consistent with pseudomembranous tracheobronchitis, and the patient was started on treatment with nebulized and intravenous liposomal Amphotericin B. Despite treatment, the patient developed signs of septic shock and died eight days later of respiratory and renal failure.

DISCUSSION

Aspergillus tracheobronchitis is an uncommon manifestation of acute *aspergillus* infection occurring in less than 7% of cases of pulmonary aspergillosis^[1]. Infection is confined to the larger airways, often with the formation of inflammatory pseudomembranes^[2]. The disease has several morphological forms^[3]. The first consists of intraluminal growth of the fungus involving more or less the entire circumference of the airway wall. Grossly, such disease may take the form of pseudomembranes lining and partially obstructing the airway lumen or completely occlusive mucus / fungus plugs. The infection is often confined to the mucosa and extension beyond the bronchial wall is unusual. Depending on the extent and location of airway disease, affected patients may be asymptomatic or complain of variable degrees of dyspnea and hemoptysis. Both patients in our report had this form of *aspergillus* tracheobronchitis, probably with an additional component of *aspergillus* bronchopneumonia.

A second morphological variety of *aspergillus* tracheobronchitis consists of one or more discrete plaques limited to a relatively small area of the airway wall. Such infection can remain localized to that site and grow within the lumen to form an obstructing mass. More commonly, the fungus invades the trachea or bronchial wall and extends into adjacent tissue. Complications include fistula formation between the airway and mediastinum, esophagus or pleura, and pulmonary artery invasion with pleural hemorrhage.

The final form of tracheobronchial aspergillosis is the least common and is seen predominantly in the smaller bronchi and bronchioles. Histologically, the abnormality is characterized by bronchocentric granulomatosis.

Unlike angioinvasive aspergillosis which typically afflicts patients who are profoundly immunocompromised, it has been suggested that *Aspergillus* tracheobronchitis is more common in mild to moderately immunocompromised patients, which may explain the endobronchial localization^[4]. Neutropenia was the underlying factor in 55 percent of patients presenting with *aspergillus* tracheobronchitis^[1]. It has also been suggested that T-cell abnormalities, such as those occurring following influenza A infection, may contribute to this form of aspergillosis^[5]. Boots *et al* reported a case of *aspergillus* tracheobronchitis in a healthy patient following influenza A infection^[5]. That patient had a persistent lymphopenia involving T cells and NK cells associated with cutaneous anergy. The disease has also been reported in patients with no known risk factors^[1]. Tracheobronchial aspergillosis has been reported in COPD patients^[6-8]. Many of these patients had

received corticosteroids or broad-spectrum antibiotics^[2]. It was found in a case control study that invasive aspergillosis, although rare in COPD, was associated with the use of high doses of corticosteroids and multiple broad spectrum antibiotics^[9]. It is possible that an alteration in the microbial flora in the airways of these patients as a consequence of broad spectrum antibiotic therapy, coupled with the immunosuppressive effects of high dose corticosteroids, predisposed to colonization and infection of their airways by *aspergillus*. Our patients were receiving both corticosteroids and broad spectrum antibiotics to treat their COPD exacerbations. Patient 1 also received a short course of oral steroids one year prior to presentation but there is no record of the second patient having received corticosteroids prior to presentation. Viral infections are a common precipitant of COPD exacerbations, but we do not know whether either of our patients had influenza or another viral respiratory tract infection as the precipitating cause of their acute illness.

Patients with *aspergillus* tracheobronchitis can be asymptomatic. The most common presenting complaints are cough, fever, dyspnea, chest pain and hemoptysis^[1,2]. They occasionally expectorate intraluminal mucus plugs^[2]. These mucus plugs can be filled with fungal hyphae^[2] and are usually culture positive for *aspergillus*. In our report, both patients complained of dyspnea and were febrile. Patient No.1 also had a history of coughing up a tracheobronchial cast that contained *Aspergillus*, many weeks after initial presentation.

The diagnosis of *aspergillus* tracheobronchitis is typically delayed because of the insidious onset, nonspecific signs and symptoms and lack of radiographic abnormalities. The radiologic picture may show only slight changes since the infection is mainly limited to the trachea and bronchi. The radiological findings range from normal to bilateral consolidation^[10]. High resolution CT characteristically shows centrilobular nodules and branching linear opacities giving a pattern known as "tree-in-bud"^[11]. Both of our patients also had bronchial wall thickening.

Treatment of *Aspergillus* tracheobronchitis is similar to that of the other forms of invasive aspergillosis. Amphotericin B is the treatment of choice. Itraconazole has also been successfully used. Nebulized Amphotericin B can also be added. Systemic steroids have no role in the treatment of *Aspergillus* tracheobronchitis. Rather steroids are a risk factor for the disease^[9]. The mortality rate is high with 43 percent patients dying despite treatment and cure achieved in only 21 percent^[11]. Our patients died of their disease, with patient No.1 improving initially but succumbing later during a

reactivation of her disease. Extrathoracic spread of disease can occur despite initiation of antifungal therapy^[1].

The diagnosis of *aspergillus* tracheobronchitis, although rare, should be considered in a patient with a COPD exacerbation who deteriorates despite receiving high dose corticosteroids and broad spectrum antibiotics. Clues to the diagnosis include the development of ill-defined nodules on the chest radiograph, centrilobular nodules with tree-in-bud appearance on high resolution CT, coughing up casts or thick mucus plugs and the bronchoscopic appearance of pseudomembranes. The diagnosis is confirmed by histopathological evidence of inflammatory pseudomembranes containing *Aspergillus* in the proximal or distal airways. Urgent treatment with systemic and possibly nebulized antifungal therapy is essential, as the mortality is high, even with prompt treatment.

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